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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/007,385	01/15/1998	HSIEN- JUE CHU	0632/0D916	4879

32801 7590 02/03/2005

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EXAMINER	
TURNER, SHARON L	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 02/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/007,385	CHU, HSIEN- JUE	
	Examiner	Art Unit	
	Sharon L. Turner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,5-8,16,18-21,23 and 24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,5-8,16,18-21,23 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10-27-04 has been entered.

2. The amendments of 7-30-04, 9-14-04 and 10-27-04 have been entered into the record and have been fully considered.

3. Claims 2, 5-8, 16, 18-21 and 23-24 are pending and are under examination. It is noted for future correspondence that claim 17, denoted as (canceled) is omitted from the complete claims listing within the 10-27-04 response.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 2, 5-8, 16, 18-21 and 23-24 are rejected under 35 U.S.C. 103(a) as set forth in Paper No. 15, 18, 26 and as set forth herein, as being unpatentable over US Patent No. 5,183,659, Timoney et al, 2 February, 1993, in view of EP0786518 A1, Hartford et al, 24 January 1997, and US Patent No. 5,597,807, Estrada et al., 28 January 1997 as further evidenced by Timoney et al., Recent advances in streptococci and streptococcal diseases (1985) pp. 294-5, Proceed. Of the IXth Lancefield Int'l Symp. on Strep. and Strep. Diseases, Japan, September 1984, Reedbooks Ltd., Chertsey.

Timoney et al, teach a live non-encapsulated attenuated S. equi strain designated strain 709-27 (ATCC 53185) which is identical to applicants S. equi strain 709-27 deposited as ATCC Accession No. 53186. Applicants argue that this strain is publicly available since 1993, see Amendment A, Paper No. 5, mailed 3-26-99, paragraph spanning pp. 2-3. This strain is applicants preferred embodiment as recited in instant claims 5, 9, 16, and 18. The page and line references cited herein are in respect to the '659 patent. Timoney teach that the vaccine may be administered either intranasally (mucosally) or orally see in particular abstract, that the vaccine is avirulent (attenuated) see in particular column 2, lines 57-64, and stimulates an immunological response which produces major IgG and IgA antibody in the nasopharyngeal mucus see in particular column 3, lines 40-45 and Figure 1. The strain is avirulent at 3X109 CFU when inoculated intranasally or orally. The strain is nonencapsulated, in particular column 4, lines 53-55. Vaccination either intranasally or orally at 3X109 CFU produced resistance to challenge with wild-type virulent strain, see in particular Figure 2. In addition, the vaccine dosages are of amounts deemed to stimulate an antibody response in the nasopharyngeal mucosa of the susceptilble horse, see in particular claims 2-3. The vaccine is protective as claimed in claims 1-4 and 9-10 and is effective

in abrogating the mortality (a symptom) associated with disease, see in particular columns 5-6.

Timoney et al do not teach the above vaccine in combination with an adjuvant/immunostimulant having the property of stimulating mucosal immunity and wherein the immunostimulant is saponin.

Hartford, EP0786518 teach a protective live attenuated nasal mucosa S. equi vaccine for protective treatment/immunization against strangles in horses. The Hartford vaccine is administered to horses in combination with an immunostimulant which comprises Quil A (saponin) adjuvant to enhance the immune response of the host, see in particular p. 3, lines 39-46. Hartford does not expressly teach that the Quil A saponin adjuvant has the property of stimulating mucosal immunity.

US Patent No. 5,597,807, Estrada et al teach Quinoa saponin compositions and methods of use. In particular, Estrada teaches Q. saponin compositions useful as immunological adjuvants, to stimulate nonspecific immunity, to enhance an immunological response to a selected antigen and to enhance mucosal absorption of a drug, see in particular abstract, column 1, lines 48-67. Estrada teaches the discovery that Q. Saponin composition can promote mucosal immunity, i.e., the production of IgG and IgA antibodies and enhances both humoral and secretory immune responses in vertebrates, including horses when administered with a selected antigen, see in particular column 5, lines 28-45 and column 6, lines 13-43. Estrada also teaches that Q. saponins enhance nonspecific immunity and cause increased absorption through mucosal membranes of desired antigenic preparations, see in particular column 6, lines 57-67. Estrada teaches that Q. saponins can be used as immunological adjuvants in vaccine compositions and as absorption adjuvants, including against selected bacterial pathogens (in vaccines), see in particular column 6, lines 13-67. Estrada teaches in

saline doses of Q. saponins at 2µg-10mg, see in particular Table 1 and with antigens of from .1-1000µg, see in particular column 8, lines 5-8.

Hartford teaches the benefit of combining a live attenuated nasal mucosa S. equi vaccine in horses with an immunostimulant adjuvant, specifically Quil A saponin as in claim 7. Estrada teaches that Quinoa (Quil A) saponins provide the properties of enhanced mucosal immunity, increased mucosal antigenic absorption and stimulation of secretory IgG and IgA antibody responses.

Thus, it would have been prima facie obvious to one of skill in the art to modify the Timoney nasal (mucosal) vaccine by adding a Quil A saponin mucosal adjuvant to achieve the beneficial effects of enhanced mucosal immunity. One of skill in the art would be motivated to perform such modifications based on the teachings of the beneficial results of the adjuvant in S. equi vaccines and the effectiveness of Quil A saponins in vaccines for producing enhanced mucosal immunity. One of skill in the art would have expected success using these methods based on the protective properties of the S. equi vaccines of Hartford and Timoney, and the beneficial results of the saponin adjuvant as taught by Hartford and Estrada in producing enhanced mucosal immunological responses. In particular, one of skill in the art would have expected the effects of stimulating an immune response, providing protective immunity and preventing at least one of the symptoms associated with streptococcus equi infection via administration to the nasopharyngeal mucosa using the claimed vaccine comprising administration of a live non-encapsulated attenuated streptococcus equi in combination with a saponin immunostimulant. As extensively set forth, the Timoney vaccine provides such properties upon administration to the nasal mucosa. The art expects that saponin would only enhance such effects. Thus, the composition, effects and method of administration to provide such effects would be obvious to the artisan at the time of

the invention in view of the cumulative reference teachings. Thus, the reference teachings render the claimed invention obvious.

Applicants argue in the response of 8-27-03 that none of the references describe a commercially successful strain and that applicants discovered that although immunogenic, the Timoney strain is not effective on its own commercially. Applicants note particular teachings of the cited references but disagree with the Examiner's case of obviousness. In particular, applicants argue that the references provide neither the suggestion for combination nor an expectation of success. Applicants argue that the rejection fails to establish that the combined materials are effective in horses since the only objective teaching for such combination in horses is the instant application. Applicants further argue secondary indica of unobviousness in the form of unexpected superiority leading to commercial success and satisfaction of a long felt need.

In contrast to Applicants conclusions, the noted improvements of the Hartford vaccine do not teach away from the positive effects of the Timoney vaccine that have already been noted. Hartford's comments speak to their perceived improvements over the Timoney vaccine, but do not negate the success of the Timoney vaccine established in the art. Applicants further argue that Hartford teaches away from saponin in that there is no specific direction to use saponin for mucosal administration. Applicants acknowledge the teaching of Hartford for an adjuvant for use in mucosal compositions, but note that the preferred compounds for such effects were noted as LT or CT toxin. Nevertheless, Hartford notes the use of adjuvants including saponin for the formulation of an immune response and in particular for an enhanced mucosal response including via administration via inhalation. Moreover, Estrada evidences that a preferred adjuvant for achieving enhanced mucosal response including via inhalation and in vaccine is the adjuvant saponin. In addition, Timoney notes that enhanced mucosal response is most

desired, see in particular Timoney II, p. 294, column 1, paragraphs 1-2. Thus, it is the cumulative teachings that suggest and provide an expectation for success of the vaccine so modified with saponin.

Applicants argue that the Li declaration (3-13-02) teaches no reasonable expectation of success. In particular, Li concludes that without testing of the saponin preparations, one would not be able to predict effectiveness without detrimental effect. However, the Li declaration fails to evidence the ineffectiveness of saponin as as a suitable adjuvant. While particular studies as referenced by Li note superior responses in particular preparations with various antigen/adjuvant combinations the resounding effects of saponin in stimulating an immune response are paramount. Hence the declaration at most provides guidance to experimentation to arrive at the most effective or beneficial combination and not to a property that is unexpected by the artisan. Moreover, the data further support that the adjuvants used and in particular saponin are readily useful in vaccine preparation and for use in stimulating immune responses to administered antigen vaccine preparations.

As to secondary indica of unobviousness, applicants argue that the Daily declaration establishes commercial success, long felt need and superiority of the invention. However, the Daily declaration merely provides sales data for Applicants product since introduced in the market. It notes that in comparison to a competitor's vaccine, sales increased while competitor's sales decreased indicating an increase in market share from 1998-1999. The declarant asserts that the increased sales further evidences the superiority of the product and fulfillment of a long felt need. In addition, Applicants argue that the comparison is made with the only available commercial product and that the commercial success of the instant product in the absence of the prior art product evidences commercial successs sufficient for patentability.

However, MPEP 716.03 notes that, "COMMERCIAL SUCCESS MUST FLOW FROM THE FUNCTIONS AND ADVANTAGES DISCLOSED OR INHERENT IN THE SPECIFICATION DESCRIPTION. To be pertinent to the issue of nonobviousness, the commercial success of devices falling within the claims of the patent must flow from the functions and advantages disclosed or inherent in the description in the specification. Furthermore, the success of an embodiment within the claims may not be attributable to improvements or modifications made by others. In re Vamco Machine & Tool, Inc., 752 F.2d 1564, 224 USPQ 617 (Fed. Cir. 1985)."

In instant case the artisan cannot determine that the commercial success of the Pinnacle vaccine does not stem from the Timoney strain, i.e., that the commercial success is attributable to the addition of saponin. No data as to the effective comparison of the prior art vaccine and the prior art vaccine modified as claimed by the addition of saponin.

Moreover, "SALES FIGURES MUST BE ADEQUATELY DEFINED. Gross sales figures do not show commercial success absent evidence as to market share, Cable Electric Products, Inc. v. Genmark, Inc., 770 F.2d 1015, 226 USPQ 881 (Fed. Cir. 1985), or as to the time period during which the product was sold, or as to what sales would normally be expected in the market, Ex parte Standish, 10 USPQ2d 1454 (Bd. Pat. App. & Inter. 1988).

While Applicants data tend to show that at a certain time period the Pinnacle vaccine sales were increasing while another commercial vaccine was decreasing, the limited data does not provide a full picture of what was happening to the full market share. While Applicants claim that their market share was increasing there is not indication of total market share of either of the vaccine preparations in comparison to any other available vaccines within the market for strangles prevention. The data is

thus not representative of market share but merely of gross sales in comparison to a competitor.

Further as to long felt need, "THE CLAIMED INVENTION MUST SATISFY A LONG-FELT NEED WHICH WAS RECOGNIZED, PERSISTENT, AND NOT SOLVED BY OTHERS. Establishing long-felt need requires objective evidence that an art recognized problemexisted in the art for a long period of time without solution. The relevance of long-felt need and the failure of others to the issue of obviousness depends on several factors. First, the need must have been a persistent one that was recognized by those of ordinary skill in the art. In re Gershon, 372 F.2d 535, 539, 152 USPQ 602, 605 (CCPA 1967) ("Since the alleged problem in this case was first recognized by appellants, and others apparently have not yet become aware of its existence, it goes without saying that there could not possibly be any evidence of either a long felt need in the . . . art for a solution to a problem of dubious existence or failure of others skilled in the art who unsuccessfully attempted to solve a problem of which they were not aware."); Orthopedic Equipment Co., Inc. v. All Orthopedic Appliances, Inc., 707 F.2d 1376, 217 USPQ 1281 (Fed. Cir. 1983) (Although the claimed invention achieved the desirable result of reducing inventories, there was no evidence of any prior unsuccessful attempts to do so.). Second, the long-felt need must not have been satisfied by another before the invention by applicant. Newell Companies v. Kenney Mfg. Co., 864 F.2d 757, 768, 9 USPQ2d 1417, 1426 (Fed. Cir. 1988) (Although at one time there was a long-felt need for a "do-it-yourself" window shade material which was adjustable without the use of tools, a prior art product fulfilled the need by using a scored plastic material which could be torn. "[O]nce another supplied the key element, there was no long-felt need or, indeed, aproblem to be solved".) Third, the invention

must in fact satisfy the long-felt need. In re Cavanagh, 436 F.2d 491, 168 USPQ 466 (CCPA 1971).

In instant case there is insufficient data to indicate that the Applicant's vaccine solved any problem that the Timoney vaccine did not already achieve, i.e., that the addition of saponin was the inventive concept resulting in the successful vaccination of strangles. Foremost it is noted that the Timoney vaccine was already established as effective in the prior art. Applicant's appear to assert that the unavailability of the Timoney vaccine is indicative of it's failure when in fact other business factors such as advertising or marketing could account for the unavailability or lack of commercial success of the prior art product.

Because the data presented is limited in scope to the placement of the sales of the Pinnacle preparation in comparison to market share and that of the prior art, the evidence of commercial success is insufficient to arise to evidence for patentability.

Estrada notes mucosal administration that is nasal. Thus, the teachings are not away as recognized by the artisan. The adjuvant saponin is established as providing enhanced immune responses via mucosal administration and via the intranasal route. Thus, there is an expectation of success as an effective antigenic adjuvant using saponin for such means. Applicants argue that there is no expectation of success based upon the use of saponin in horses with the noted vaccine. This is true, as such reference would arise to a 102 rejection. Yet the cumulative teachings suggest this modification. Applicants argue that the Li declaration speaks to the unobviousness of the invention as combined with saponin for use in horses. Yet the declaration merely established differences in effects with different species, immunogenic vaccines and adjuvants. Yet the evidence does not establish a general recognition that saponin is non-immunogenic or non-immunogenic in horses. The publications in contrast speak to

the general recognition within the art that saponin functions as an immune enhancing agent in various vaccine preparations and amongst different species.

Applicants further argue there is no expectation of success. Applicants additionally argue hindsight reconstruction by the examiner and particularly argue that the combined references do not provide for the enhanced protective immunological effect demonstrated by the claimed saponin/attenuated S. equi vaccine. Applicants argue and submit a declaration by Dr. Li to provide evidence of non-obviousness as to a vaccine which induces an immune response and which is protective in horses. The relevancy of an antibody response and adverse side-effects are also discussed. Applicants argue and submit a declaration as to the inability to extrapolate the data in mice to effects in horses and to establish protective immunity based upon data such as antibody response. Applicants arguments and declaration outline three bases for rejection, which are not directly on point as expressed by the Examiner, see previous rejection of record.

Applicant's arguments and declaration filed 3-13-02 have been fully considered but they are not persuasive. Applicants arguments as to a "demonstration of an enhanced immunological effect" is not recognized by the Examiner as it is noted that no direct comparison of the Timoney vaccine with and without saponin or other adjuvants has been conducted. As previously noted, the vaccine of Timoney is already recognized for its protective properties, see in particular claims. Thus the protective effect of the vaccine does not appear to be in question. The question of relevancy is whether or not the artisan would have found it obvious to combine the Timoney vaccine with saponin to arrive at the composition claimed as well as the method of stimulating an immune response with the modified composition claimed. In this respect, the literature is clear based on Hartford and Estrada that amongst other adjuvants,

saponins are recognized to stimulate an immune response upon administration that is generally more beneficial than the selected antigen presented alone. Thus, the cumulative reference teachings would only be expected to improve the immune response and protection achieved via the Timoney vaccine with the combination of saponin. As to amended claims 22 and 23, it is noted that the composition is suitable for nasal administration as set forth in Timoney and that the vaccine is effective to provide protective immunity following challenge as noted in column 5-6 of Timoney the vaccinated horses which would be naturally exposed to S. equi challenge would have been expected to have strangles occurrence in 40% of the horses by at that date, only 2 horses exhibited disease. The comments of the previous action are appended for completion.

In paragraphs 1-2 of the traversal on 3-13-02 Applicants argue that Timoney is silent as to adjuvants and thus it is not obvious from Timoney to use saponin as an adjuvant. Applicants argue that absence a suggestion that the adjuvant saponin has immunostimulatory properties and that such an adjuvant would provide a protective immune response to challenge to disease one would not be motivated to modify Timoney to arrive at the invention.

In response, Hartford suggests that the adjuvant saponin has immunostimulatory properties such that it provides a protective immune response against disease challenge. In particular, Hartford teaches protection via a live attenuated nasal mucosa S. equi vaccine in combination with an immunostimulant that comprises Quil A (saponin) adjuvant to enhance the immune response of the host to the invading pathogen, see in particular p. 3, lines 39-46.

In paragraph 3 of the traversal on 3-13-02 Applicants argue that Hartford and Estrada do not remedy the deficiencies of Timoney, in particular that Quil A (saponin) is

but one adjuvant included in the deletion vaccine of Hartford but that such adjuvant is not exemplified. Applicant's argue that Hartford does not teach or suggest that any adjuvant stimulates mucosal immunity and does not teach or suggest that Quil A is an immunostimulatory adjuvant.

In response, Hartford does teach that Quil A is a known adjuvant that stimulates the immune system and enhances the immune response of the host, see in particular p. 3, lines 39-46. In addition, Estrada specifically teaches that saponins Quillaja and Quinoa stimulate IgG and IgA, mucosal specific immunity, see in particular Estrada, Figures 1-6, and columns 5-8.

In paragraph 4 of the traversal on 3-13-02 Applicants argue that Estrada also fails in that Quinoa saponin is but one specific type of saponin that surprisingly stimulates an immune response when administered mucosally, but that Estrada does not use S. equi or a comparable antigen and thus Estrada does not teach or suggest that an immune response may be achieved using the combination of Quinoa saponin and S. Equi or a comparable bacterial or disease causing antigen. Applicants further argue that neither does Estrada teach that Quinoa saponin provides protection from infection in the face of challenge.

In response, Estrada is not solely relied upon for such teachings. It is Hartford and Estrada which in particular cumulatively teach that Quillaja (Quil A) and Quinoa saponins are effective in stimulating immunity including mucosal immunity as evidenced by production of IgG and IgA as exemplified in Estrada and in promoting S. equi specific immune responses as is taught by Estrada, column 5, line 36-column 6, line 52 and Hartford p. 3, lines 39-46, Examples 1-IV, Results and also the Conclusion.

In paragraphs 5-8 of the traversal on 3-13-02 Applicants argue that Estrada's teachings are unexpectedly different than Quil A saponin and thus that there is no

reasonable expectation that such adjuvants would provide an enhanced immune response or protection in horses. Applicants acknowledge that Estrada teaches Quinoa saponin increased IgG and IgA, however they subsequently argue that such an immunological response is not predictive of protective immunity in the face of challenge. Applicants submit that the artisan knows that there is no definite correlation between the presence of antibodies and protective immunity as demonstrated in the specification at pp. 15-16 of the specification and that if the levels are not predictive then there is no expectation of enhanced protective effect with adjuvant. Applicants acknowledge that Estrada causes increased absorption through mucosal membranes but argue that the reference does not teach or suggest that saponin stimulates protective mucosal immunity in challenge and thus that there is no reasonable prediction of protection provided by immunization with Quinoa saponins.

In response, it is unclear how Estrada's teachings are still considered unexpected with respect to Quil A as Estrada notes IgG and IgA production via Quillaja and Quinoa saponins. While Estrada notes that IgA responses had not yet been noted for Quillaja, Estrada clearly shows that as of at least 1-28-1997 IgA and IgG stimulation are known for Quillaja and Quinoa saponins and would not be unexpected as of the filing date of instant '385, 1-15-1998. Applicant's arguments with respect to the predictability of the immune response upon challenge is jointly addressed in Timoney, Hartford and Estrada. For example, instantly claimed vaccine (live non-encapsulated attenuated S. equi) is the same as Timoney with the sole exception of saponin adjuvant. Timoney has already established in the art that the claimed live non-encapsulated attenuated S. equi vaccine stimulates the appropriate immune responses such that protective immunity is established in the host in response to challenge, including IgG and IgA even without adjuvant, see in particular Figures 1-3, Columns 5-6 and Claims

1-10. Thus, the specificity of the vaccine is established. It is known in the art as exemplified by Hartford and Estrada that Quillaja and Quinoa saponins are adjuvants which enhance antigen specific immune responses in the host when co-administered with the appropriate antigens, and that saponins predictably and specifically stimulate mucosal immunity through enhanced mucosal absorption and production of antigen specific IgG and IgA, see in particular Hartford, p. 3 and Estrada, columns 5-6, as noted above. Thus, the predictive effects do not appear to be of question. It is also noted that sero conversion per. se., is not required but merely IgG and/or IgA mucosal production. The artisan would expect only improved vaccination effects by inclusion of a saponin adjuvant with the Timoney vaccine, the specificity of the vaccine already having been established by Timoney.

In paragraph 9 of the traversal on 3-13-02 Applicants argue that Estrada does not teach the use of S. equi or other bacterial or disease causing antigens but that Estrada uses avidin and cholera toxin which are known adjuvants as exemplified by Hartford, p. 3, lines 39-44. Applicants conclude that thus Estrada teaches non-specific immunological responses to adjuvants by administration of saponin and that the artisan could not predict protection against contact with a specific disease based on Estrada's teachings.

In response, it is not Estrada's teachings that are solely relied upon, but the cumulative teachings of Timoney, Hartford and Estrada as set forth above.

In paragraphs 10-11 of the traversal on 3-13-02 Applicants argue that the artisan could not predict a protective immune response using any saponin type, in particular as Estrada teaches the benefits of Quinoa saponin which are unexpectedly different from Quillaja saponin. Applicants again argue that Estrada fails to use disease specific antigen and that Quinoa saponins rather than Quillaja saponins enhance nonspecific

immunity and cause increased absorption through mucosal membranes. Evidence of unexpectedness is noted at col. 2, lines 25-27 and that thus the artisan could not expect the properties of any type of saponin used as an adjuvant. Based on the aforementioned teachings Applicants conclude that Estrada does not supply the suggestion or motivation missing from Hartford and Timoney to render the invention obvious.

In response, as noted above Estrada is not unexpected as of the patent publication date. The benefits of Quillaja and Quinoa saponins in the stimulation of enhanced mucosal immunity as exemplified by enhanced mucosal absorption, IgG and IgA production are noted in Estrada. The specificity of the Timoney vaccine is established. Hartford also suggests the inclusion of adjuvants for enhancing the immune response in S. equi vaccination of animals, and specifically for mucosal immunity. Thus, Estrada and Hartford both provide suggestion and motivation to modify the Timoney vaccine by inclusion of saponin adjuvants.

In paragraphs 12-15of the response of 3-13-02, Applicants note the Examiner's previous assertion that Timoney at col. 6, lines 30-31 teach that "the mouse has historically been the model for the immunology of S. equi infection." However, Applicants conclude that all this teaches is the study of the immune response in mice to potential equine vaccines. Applicants argue that Timoney did not extrapolate the data in mice to conclude or suggest a similar effect in horses. Applicants argue that Hartford did not establish protective effects in horses, but only in mice using the mouse model. Applicants again suggest that Hartford did not extrapolate or suggest similar effect in horses. Applicants further argue that even though Hartford did test the vaccine in horses, the test was only for safety and not efficacy, and that the artisan could not conclude efficacy without actually performing the tests in horses. Applicants argue that

the Examiner's conclusion of intrinsic immunity is not supported by the reference teachings and is constructed by hindsight reasoning and that the artisan could, at best only be motivated to combine Hartford, Estrada and Timoney based on the present invention because Timoney is silent to adjuvants which would provide the enhanced protective immunological effect demonstrated by the claimed saponin and the attenuated S. equi vaccine.

In response, it is noted that Timoney not only suggests that the mouse model is capable of extrapolation to horses, Timoney shows that it is extrapolatable by showing that the protective effects in horses are indeed exemplified in mice. In particular, Timoney directly compares in a "parallel test of efficacy" horses and mice, see in particular column 5, line 7-column 6, line 5 and column 6, line 29-line 54. Hartford also includes experimentation in mice, and horses. Hartford's safety, treatment, vaccination/challenge and protection studies are directed to both mice and horse vaccines, but are especially contemplated for use in treatment of horses, see in particular p. 2, lines 1-49 and p. 3, lines 6-10, "the invention further provides a live vaccine for combating Streptococcus infection in horses." In addition, to the experimentation in mice, (see in particular Examples III-IV), Example V, teaches that the protective results noted in mice are comparable those noted in horses. In particular, six horses were inoculated and followed to 4 weeks post/challenge. No mortality nor clinical signs of infection were noted, in particular there were no sudden temperatures nor abscesses formed in the mandibular and pharyngeal lymph nodes, see in particular p. 12, Clinical signs and Post-mortem examination. Thus, the prevailing evidence of the references establishes, even in the safety studies of Hartford, that prior to Applicant's invention, the S. equi vaccines or the prior art were known to be similarly protective and predictive in both horse and mouse models as disclosed.

Finally, in paragraph 16-20, of 3-13-02 Applicants point to the declaration of 6-29-01 and conclude therefrom that the invention is thus not obvious in light of Timoney, Hartford and Estrada, alone or in combination. In particular, that the prior art fails to render obvious that the S. equi vaccine when combined with saponin, would exhibit enhanced immunostimulatory and protective effects as a result of the addition of saponin.

Applicant's declaration filed 6-29-01 has been fully considered but is not persuasive. In particular, the Examiner notes that the comparison delineated in the declaration is between the instantly claimed vaccination and a commercial vaccine of Carbopol/S. equi enzyme extract administered intra-muscularly. Such evidence is insufficient to show an unexpected difference in the vaccine of Timoney and the vaccine of Timoney when modified by the inclusion of saponin, particularly as the Timoney, Hartford and Estrada reference teachings cumulatively suggest that the saponins' inclusion would specifically enhance the protective immune response stimulated by the Timoney vaccine alone. Additionally, it is noted that there is no evidence of record which would contradict the efficacy of any adjuvant or of saponin in particular from exhibiting such effects, in particular as noted for the benefits of mucosal administration and immunity.

Although not relied on for the rejection, it is again noted that the skilled artisan recognizes as set forth in Timoney et al., Recent advances in streptococci and streptococcal diseases (1985) pp. 294-5, Proceed. Of the IXth Lancefield Int'l Symp. on Strep. and Strep. Diseases, Japan, September 1984, Reedbooks Ltd., Chertsey, that cumulative findings suggest that successful vaccination requires stimulation of the nasopharyngeal immune response and that vaccination with 709-27 stimulates IgA and IgG antibodies even in the absence of Q. Saponin adjuvant, see in particular Figure 1.

The references cumulatively provide both the suggestion of making the invention and an expectation of success. Therefore the claimed invention is rendered obvious to the skilled artisan at the time of the invention.

It is further noted that the amended language "for providing protective immunity against Streptococcus equi infection following Streptococcus equi challenge" is non-limiting to the composition and similarly contributes no further steps in any methods as recited. The limitation is akin to a recitation of intended use without the addition of further limiting active steps. However, to the extent to which the recitation implies that the method be administered "following Streptococcus equi challenge", it is unclear that applicants have support for such language as no support was provided by page and line number at the time of entry. For search and examination purposes the recitation has received no weight. The recitation "for providing protective immunity against Streptococcus equi infection" is non-limiting but has been specifically addressed in the rejection above as the vaccine of Timoney has already been found to provide protective immunity against Streptococcus equi infection regardless of the addition of adjuvant. The above discussions exhibit that the artisan would expect increase the protective immunity/antibody response/prevention of symptoms already provided by the Timoney vaccine.

Applicants additionally argue in the response of 11-12-02 that the Examiner's rejection fails to establish that the combined materials are effective in horses, since the only objective suggestion for such a combination in horses in found in the instant application. In addition Applicants present arguments as to indicia of unobviousness in unexpected superiority (of the vaccine) leading to commercial success and satisfaction of a long felt need. In particular Applicants submit a declaration under 37 CFR 1.132 of

Robert Daily to establish commercial interest, success and long felt need of the claimed invention that is argued to result from the superiority of the claimed invention.

In response, the PTO has insufficient facilities for testing or comparing multiple vaccine preparations. While the Examiner's rejection fails to definitively establish that the combined materials are effective in horses, this does not appear to be a grounds for removal of the rejection of record. The Examiner has not questioned the findings of Applicants specification that the combined materials are effective in horses. Instead, the Examiner has presented a case whereby such findings are obvious in light of the cumulative prior art teachings. The comparison of the prior art vaccine with or without adjuvant has yet to be performmed by Applicants and presented to the Office for consideration. As to the objective suggestion for the combination of materials in horses, the Examiner relies on the cumulative reference teachings of Timoney, Hartford and Estrada as extensively discussed in the record. In reiteration of above, it is noted that Timoney not only suggests that the mouse model is capable of extrapolation to horses, Timoney shows that it is extrapolatable by showing that the protective effects in horses are indeed exemplified in mice. In particular, Timoney directly compares in a "parallel test of efficacy" horses and mice, see in particular column 5, line 7-column 6, line 5 and column 6, line 29-line 54. Hartford also includes experimentation in mice, and horses. Hartford's safety, treatment, vaccination/challenge and protection studies are directed to both mice and horse vaccines, but are especially contemplated for use in treatment of horses, see in particular p. 2, lines 1-49 and p. 3, lines 6-10, "the invention further provides a live vaccine for combating Streptococcus infection in horses." In addition, to the experimentation in mice, (see in particular Examples III-IV), Example V, teaches that the protective results noted in mice are comparable to those noted in horses. In particular, six horses were inoculated and followed to 4 weeks post/challenge. No

mortality nor clinical signs of infection were noted, in particular there were no sudden temperatures nor abscesses formed in the mandibular and pharyngeal lymph nodes, see in particular p. 12, Clinical signs and Post-mortem examination. Thus, the prevailing evidence of the references establishes, even in the safety studies of Hartford, that prior to Applicant's invention, the S. equi vaccine of the prior art were known to be similarly effective to evoke an immune response, protective against mortality (a symptom) and predictive in both horse and mouse models as disclosed.

Applicant's 37 CFR 1.132 declaration via Robert Daily has also been fully considered but is not persuasive. As to the declaration Point 4 speaks to the commensurate scope of the product Pinnacle TM with the claimed composition and route of administration. Point 5 speaks to increases in units sold and gross sales since the products introduction into the market along with a decrease in sales of a competitive killed S. Equi product and state that the decrease in sales of the killed vaccine resulted from entry of Pinnacle TM to the commercial market. Point 6 concludes that the sales data establish commercial succes and significant impact in the market. The declaration statest that Pinnacle provides a safe and effective alternative to traditionally reactive intramuscular vaccines and that the increased sales reflect product superiority. The declaration states that the commercial success results from the attenuated bacterium combined with saponin.

In response to points 5 and 6, the comparison presented is between sales data for Pinnacle ^{TM} (which is representative of the claims although the dosage is not noted) and a Bayer killed S.equi product. The data notes that since Pinnacle's introduction to the market, units sold and gross sales have increased while in the third quarter of 1999 sales of the Bayer product declined from the prior year coinciding with entry of Pinnacle to the commercial market. While this data tends to support increased market share, the

evidence of record is insufficient to conclude such as there is no disclosure of the corresponding variables for the remainder or even to a large proportion of the total market. For example sales may increase due to the price per unit being cheaper than the competitor or due to aggressive marketing tactics. Yet more importantly the comparison presented is not one of the claims in comparison to the closest prior art as set forth in the rejection, i.e., Timoney that is the claimed vaccine but without the combination of saponin. The MPEP notes that commercial success must flow from the functions and advantages disclosed or inherent in the description in the specification and may not be attributable to improvements or modifications made by others, see in particular MPEP 716.03(b) and In re Vamco Machine & Tool, Inc., 752F.2d 1564, 224 USPQ 617 (Fed. Cir. 1985). There is no evidence as to what market share or commercial success the Timoney vaccine enjoys. Moreover, the Timoney vaccine is already recognized as a solution to S. equi infection. The invention by Applicants is a supposed improvement of Timoney by the addition of saponin. Yet even here the improvement is deemed to be the invention of another because Hartford and Estrada have already taught the addition of saponin to S. equi vaccines so as to enhance the immune response. The modification claimed is a solution already recognized in the art for the same noted properties. As no comparison of the instant vaccine with the vaccine of Timoney has been performed, no conclusion of non-obviousness can be concluded. All the specification appears to add is evidence that the expected properties are provided. Moreover, Applicants arguments as to long felt need do not appear to arise to evidence of non-obviousness because S. equi vaccines are known as for example in the Timoney vaccine, are in practice and are known to be successful. Thus, Applicants arguments and the declaration are insufficient to overcome the obviousness rejection of record.

In the RCE of 10-27-04 Applicnant's request further consideration of the arguments presented 7-3-04 and 9-14-04. With respect to the first point denoted at pp. 5-7 of the response, Applicants stress that suggestion or motivation is not provided with respect to nasal mucosal administration. Applicants attempt distinction of inhalation via mouth. Applicants assert Estrada fails to evidence mucosal immunity. Applicants argue that Hartford does not evidence specific experiments with Quil A and that at best the combination might teach saponin administration via other than the mucosa.

These arguments have been fully considered but are not persuasive. The full teachings of the prior art references are relevant in full and in contrast suggest and motivate the artisan to use Quil A saponin to enhance mucosal immunity via administration to the nasal or oral mucosa which is in fact contiguous as recognized in the art. Moreover inhalation is encompassing to either intra nasal, mouth or oral administration. Accordingly, no distinction as argued by applicants is found. Furhter Estrada does evidence stimulation of mucosal immunity as evidenced via IgA for example. The fact that Hartford does not teach a specific experiment using Quil A is immaterial to the full reference teaching relied upon which specifically delineate Quil A as a suitable adjuvant for nasal administration of S. equi vaccine.

With respect to the second point denoted at pp. 7-11 of the 10-27-04 response, Applicant's stress that motivation and expectation are not provided particularly in that Estrada is not relevant to vaccination in horses. Applicants note the cited case law asserting that the combination as set forth is merely one of "obvious to try" or and further suggesting that the motivation and expectation of success are not provided in the prior art. Applicants assert that the Examiner did not consider the Li (3-13-02) declaration of which they presume evidences the unpredictability of saponin's

effectiveness in horses and assert no prima facie case of obviousness has been made. Applicants further point to Exhibit 1 as evidence of non-obviousness.

In response, Estrada is on point to horses, see in particular column 5, lin3 30, "hoses". In contrast, motivation and expectation of success are noted and a prima facie case of obviousness has been shown. With respect to Li, the Examiner noted consideration of the declaration. However, the declaration was not found to be persuasive because the probative studies did nothing to teach away from the teachings of saponin antigen/adjuvant combinations and their primarily resounding effects of stimulating immune responses. Further Li's comments with respect to opinion fail to evidence unexpected results. Safety is a consideration but adverse responses to immunogen are widely known but tolerated in part because these effects do not negate the benefits of positive stimulation of the immune response. Hence the declaration at most provides guidance to experimentation to arrive at the most effective or beneficial combination and not to a property that is unexpected by the artisan. Moreover, the data further support that the adjuvants used and in particular saponin are readily useful in vaccine preparation and for use in stimulating immune responses to administered antigen vaccine preparations. With respect to Exhibit 1, the Jacobs reference is noted to disclose administration with the TW928 (live non-encapsulated attenuated) vaccine of the claims, see in particular p. 564. However, the administration is not noted to be with saponin as instantly claimed. It is true that an inactivated whole cell vaccine was administered with saponin. However, this vaccine is not the subject of the claims and not appropriate to provide evidence of unobviousness via comparison as the immunizations differ in components and cannot be compared. The fact that the instant vaccine was not exemplified in combination with saponin does not detract from the

motivation and expectation set forth showing a prima facie case of obviousness. If the experimentation had been performed it would have been a 102 rejection.

With respect to the third point denoted at pp. 11-14 of the 10-27-04 response, Applicants now make clear that the Timoney vaccine, "is not, nor was ever, commercially available." On this point it is unclear how Applicants can evidence commercial success sufficient to overcome the rejection.

MPEP 716.03 makes clear that the commercial success must be derived from the claimed invention. "In considering evidence of commercial success, care should be taken to determine that the commercial success alleged is directly derived from the invention claimed, in a marketplace where the consumer is free to choose on the basis of objective principles, and that such success is not the result of heavy promotion or advertising, shift in advertising, consumption by purchasers normally tied to applicant or assignee, or otherbusiness events extraneous to the merits of the claimed invention, etc. In re Mageli, 470 F.2d 1380, 176 USPQ 305 (CCPA 1973) (conclusory statements or opinions that increased sales were due to the merits of the invention are entitled to little weight); In re Noznick, 478 F.2d 1260, 178 USPQ 43 (CCPA 1973). In ex parte proceedings before the Patent and Trademark Office, an applicant must show that the claimed features were responsible for the commercial success of an article if the evidence of nonobviousness is to be accorded substantial weight. See In re Huang,100 F.3d 135, 140, 40 USPQ2d 1685, 1690 (Fed. Cir. 1996) (Inventor's opinion as to the purchaser's reason for buying the product is insufficient to demonstrate a nexus between the sales and the claimed invention.). "

In this analysis, the only difference between the claimed invention and the invention of the prior art is the addition of saponin immunostimulant. The prior art already acknowledges the benefits of the live non-encapsulated attenuated S. equi.

Hence the commercial success must be derived from the addition of adjuvant for the evidence to be accorded substantial weight. Yet here it is now clear that the consumer was never even at liberty to purchase the vaccine of the prior art known to be useful and therefore Applicant's referral to the commercial success accorded their product does not appear to be the result of commercial success over the prior art product afforded via saponin but merely the commercial availability for the first time of an art accepted vaccine recognized as having benefit in treating infected horses. Accordingly no further comparison seems relevant nor possible as noted by Applicants. However, the evidendence is not deemed sufficient to evidence commercial success sufficient to overcome the 103 obviousness rejection of record as the commercial success does not appear to stem from the addition of saponin but merely from the availability for the first time of the prior art vaccine via purchase. Many business considerations may be the cause of the prior art vaccine being unavailable commercially. The 103 is supported via both motivation as well as an expectation of success recognized in the prior art.

Further while Applicants point to subsequent experimentation towards the arrival of the optimal vaccine formulations, noted contraindications and recoommendations for vaccination (exhibits 2-7), such does not counter the obviousness rejection of record. Certainly the artisan would continue experimentation to arrive at the most optional formulations for vaccination with some being more successful than others. However, such does not evidence non-obviousness to the prior art recognition of intranasal administration or the addition of saponin for vaccine delivery. The success of the prior art vaccine was documented via Timoney, and hence long felt need is not evidenced. The commercial success merely appears to stem from the commercial availability of the prior art product for the first time and proper motivation and expectation of success are noted to the claim limitations which comprise the supposed improvements.

With respect to the fourth point noted at pages 14-15 of the 10-27-04 response, Applicants argue that Exhibit 1 evidences that the intranasal administration of the Hartford vaccine is not protective and that studies in mice while valuable does not preclude the necessity for studies in horses. To clarify, the Examiner is not requiring this comparison, nor is it clear how such would obviate rejection. The Exhibit compares several vaccine preparations via different routes. However, no basis is apparently provided via Exhibit 1 for withdrawal of the obviousness rejection of record.

With respect to the fifth point at p. 15 of the 10-27-04 response Applicants take note that the phrase "following S. equi challenge is supported as delineated in the response. However, no new matter rejection is of record with respect to the language and the support provided does not appear to further any point for withdrawal of the obviousness rejection of record. As to the language with respect to the claim, the Examiner merely points out that the language is one of intended use and bears no patentable distinction to the composition itself.

Applicants arguments and Exhibits of 10-27-04 have been fully considered but are not persuasive for withdrawal of the obviousness rejection of record for the reasons set forth above. Accordingly, rejection is maintained.

Status of Claims

6. No claims are allowed.

Conclusion

7. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE**

FINAL even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (571) 272-0894. The examiner can normally be reached on Monday-Friday from 8:00

AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached at (571) 272-0961.

Sharon L. Turner, Ph.D.
February 2, 2005

SHARON L. TURNER, PH.D.
PATENT EXAMINER
2-2-05